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Analytica Chimica Acta 597 (2007) 129–136

ANALYTICA CHIMICA ACTA

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# A three-factor Doehlert matrix design in optimising the determination of octadecyltrimethylammonium bromide by cation-exchange chromatography with suppressed conductivity detection☆

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Received 22 March 2007; received in revised form 14 June 2007; accepted 15 June 2007
Available online 22 June 2007

Paper dedicated to Prof. P.G. Zambonin on the occasion of his 72th birthday.

## Abstract

A simple and effective chromatographic method with suppressed conductivity detection was developed and validated to determine dissolved samples of octadecyltrimethylammonium bromide ($C_{18}H_{37}N^+Me_3Br^-$, ODTAB) for purity testing. A response surface methodology generated with a Doehlert matrix design was applied to optimize the chromatographic and detection conditions in ion-exchange chromatography (IEC) with conductivity detection in the chemical suppression mode. A three-factor Doehlert design was performed to fit a second-order model and jointly optimize the peak intensity and shorten analysis time through a global desirability function. Regenerant flow rate, volume fraction of acetonitrile in the acidic eluent and its flow rate were studied at seven, five and three levels, respectively. The optimized separation and detection conditions were accomplished by using a cation-exchange column eluted at 0.5 mL min$^{-1}$ with an isocratic mobile phase composed of $CH_3CN$ and 25 mN $H_2SO_4$, 82/18 (v/v). Chemical suppression of ionic conductivity was performed by 100 mN tetrabutylammonium hydroxide (TBAOH) as a regenerant at a flow-rate of 4.0 mL min$^{-1}$. Remarkably good agreement was found between predicted and experimental values of signal intensity and chromatographic retention. With the developed method, a linear calibration curve of ODTA$^+$ as bromide salt from 5 to 1000 ppm was obtained using hexadecyltrimethylammonium bromide as internal standard. The estimated limit of detection was 0.3 ppm (S/N = 3). The effectiveness of electrochemically suppressed conductivity detection of ODTA$^+$ was also demonstrated, thus making easier the whole detection operation and instrumental needs as well.

*Keywords:* Experimental design; Doehlert design; Chemometrics; Surfactant; Octadecyltrimethylammonium ion; Ion chromatography; Suppressed conductivity detection

## 1. Introduction

Cationic surfactants such as quaternary ammonium compounds are prepared by treatment of an amine with an alkylating agent. The alkyl chain length of a surfactant has a significant influence on its physicochemical properties and hence on various chemical and biochemical applications. Ionic surfactants are frequently used as antimicrobial, emulsifying, anticorrosion and softening agents in pharmaceutical preparations, cosmetic formulations, cleaning products, disinfectants and other industrial manufactures [1]. Cationic surfactants are in general more expensive than anionics such as sulfonates or sulfates, and are used only in applications in which they cannot be substituted by other surfactants, i.e. those which require a positive charge or a bactericide action. Octadecyltrimethylammonium (ODTA$^+$) bromide is an antiseptic agent with detergent properties. It has the wide spectrum of antiinfectives against bacteria and fungi. It is used as an antistatic agent, foam depressants, cosmetics and textile softeners as well as an ingredient of shampoos for treating seborrhoea and psoriasis. Alkyl ($C_{16}$, $C_{18}$,

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☆ Presented, in part, at the XXII Congresso Nazionale della Società Chimica Italiana, SCI 2006, 10–15 September 2006, Florence (Italy), poster ANA-P-24.

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0003-2670/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.aca.2007.06.038

$C_{22}$) trimethylammonium chloride is currently authorized as preservative up to a maximum concentration of 0.1%. Very recently, the European Commission has received a submission from industry proposing that cetrimonium ($C_{16}$), steartrimonium ($C_{18}$), and behentrimonium ($C_{22}$) chloride can be used at higher concentrations (i.e., >0.1%) for non-preservative purposes [2]. Indeed, the Scientific Committee on Cosmetic Products is asked to assess the risk to consumers when alkyl ($C_{16}$, $C_{18}$, $C_{22}$) trimethylammonium salts are used in cosmetic products.

The analytical methods developed for quaternary ammonium compounds, with respect to the uniformity of the alkyl chain, suffer for some limitations which arise both from the separation and detection conditions [3–10]. The latest issue is especially true for the analysis of non-aromatic surfactants which have no properties of natural UV absorption or fluorescence. As far as the separation, long alkyl chain trimethylammonium surfactants can be separated by ion-pair chromatography with non-polar stationary phases using chromophoric eluents and indirect UV detection [3]. In ion-pair liquid chromatography, however, the resolution is frequently poor owing to problems associated with strong sorption, or incomplete separation and peak tailing of long chain surfactants. Capillary electrophoresis (CE) as a separation tool of cationic surfactants has also been evaluated [6], but the occurrence of a strong adsorption of these substances at the inner surface of the fused silica capillary and the well-known detection drawbacks of CE are not overcome easily.

Taking advantage of the inherently ionic character of $ODTA^+$, a cation-exchange column was chosen as a means to chromatographically separate the quaternary ammonium surfactant [11,12]. Classically, the attainment of the optimized experimental conditions is performed by varying each experimental parameter independently of the others. Although such a univariate strategy may appear the simplest approach, this is not the correct way to avoid pitfalls during an experimental work. A multivariate strategy represents the best solution to perform the optimization of the variables, thus conducting a more thorough investigation of the method than the common step-by-step procedure [13]. Accordingly, in this work, a chemometrical approach was considered to optimize the most important experimental parameters governing the suppressed conductivity detection, using tetrabutylammonium hydroxide (TBAOH) as a chemical regenerant. Besides the regenerant flow rate, two additional variables examined in ion-exchange chromatography were the eluent flow rate and the content of acetonitrile in the acidic mobile phase. The application of a factorial design such as a Doehlert matrix was well-suited to optimize the separation and detection of the $ODTA^+$ with a reduced number of experiments [14,15]. The aim was to get high sensitivity and short analysis time. Most notably, one of the main feature of the Doehlert matrix design is that it is more efficient and needs fewer experiments than other factorial designs such as central composite (CCD) and Box-Behnken (BBD) and allows the selection of different levels (e.g., 3, 5 and 7) of individual variables [16–21]. Furthermore, the whole experimental domain is explored through a minimum of experiments as the design is composed of 13 uniformly distributed points in the experimental domain (see Fig. 1). The factor that has higher influences is studied at more number of levels and that with least effect at lower levels. Here, regenerant flow rate, volume fraction of acetonitrile and eluent flow rate were studied at seven, five and three values, respectively. Subsequently, the acidic concentration in the eluent solutions, the column temperature and the use of electrochemical suppression were tested to improve the method in terms of sensitivity and limit of detection. The results obtained were finally subjected to a statistical analysis to assess the method linearity, repeatability and reproducibility. This study brings additional evidence that under proper experimental conditions of stationary and mobile phases, cation-exchange chromatography with suppressed conductivity detection is a very useful analytical method to establish the quality product of ODTAB samples.

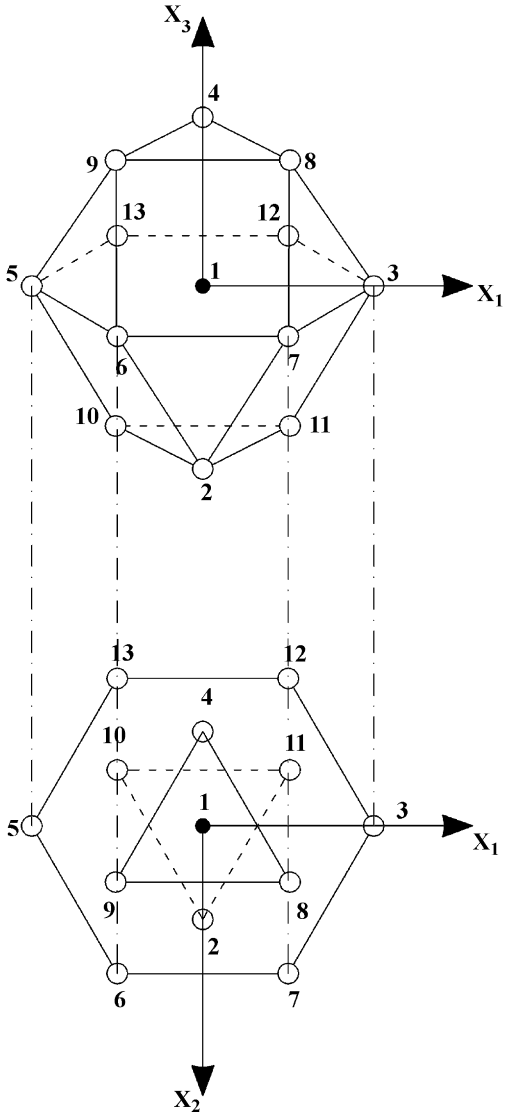

Fig. 1. The scheme of Doehlert design composed of 13 uniformly distributed points in the experimental domain and two extra points at the center of the design. Experimental variables: regenerant flow rate in the chemical suppression mode ($X_1$), percentage of ACN in the acidic eluent ($X_2$) and eluent flow rate ($X_3$).